ARENA
APPLIED RESEARCH ETHICS NATIONAL ASSOCIATION

On behalf of the Applied Research Ethics National Association (ARENA), we appreciate the opportunity to comment on the submission and IRB review process related to adverse events information discussed in the Federal Register, February 8, 2005, Volume 70, Number 25. ARENA is the membership division of Public Responsibility in Medicine and Research (PRIM&R). PRIM&R is an educational organization dedicated to creating, implementing, and advancing the highest ethical standards in the conduct of research.

ARENA's mission is to enhance human and animal research subject protections and the responsible conduct of research through the educational and professional development of its members. Members represent a diversity of institutions throughout the world whose research efforts vary substantially. ARENA's membership includes a range of professionals from research administrators, government officials, and academic deans, to members and chairs of Institutional Review Boards (IRBs), Institutional Animal Care and Use Committees (IACUCs), and Institutional Biosafety Committees (IBCs). We have the following comments to offer on this proposed rule:

Question 1. What role should IRBs play in the review of adverse events information from an ongoing clinical trial?

The role of the IRB is to ensure that the rights and welfare of research subjects are protected. The review of all adverse events in an ongoing clinical trial by a scientifically founded body is extremely important in providing knowledgeable protection for subject safety and welfare. To do this, the IRB needs substantive, meaningful data throughout the conduct of all clinical trials.

For ongoing clinical trials, the role of the IRB should be to ensure there is an adequate data safety monitoring plan in place at the time of initial review and confirm that the plan is working at all continuing reviews. Federal regulations state that "Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects." 21 CFR 56.111(a)(6). In addition, NIH policy consistently recommends that all clinical trials include a data and safety monitoring plan. NIH further indicates that the monitoring plan should be tailored to the nature, size and complexity of the clinical trial. (NIH Policy for Data and Safety Monitoring, Release date: June 10, 1998).

The role of the IRB should be to review the data safety monitoring plan to ensure that there is communication between the Principal Investigator, the Sponsor, and the IRB. This plan would set the stage for the local IRB to manage adverse and unanticipated events. The plan should describe the data monitoring system, which typically is centralized across research sites, and includes procedures for assessing risk to research subjects and recommending actions as needed. The plan should specify who will do the evaluations, the data that will be evaluated, the frequency of the evaluations, stopping rules, and the process for communicating the results of the evaluation to the IRB.

The role of the IRB in reviewing unanticipated events should be no different than the review of any piece of information that impacts the rights and welfare of subjects. At the initial review of a protocol, the IRB expects the Principal Investigator to include procedures for subject safety, provisions to minimize risks, and methods for data analysis that can be presented in a useable format to the IRB. Only then can the IRB make sound judgments about whether the research procedures meet the federally mandated criteria for approval. As the IRB provides continuing oversight of the research, it needs to similarly receive complete and useful information that can be used for ongoing risk assessment. This information must include a summary report of adverse events (serious, unanticipated, and reasonably related) with a description of how these were

handled since the last IRB review of the research. Obviously, it would continue to be the responsibility of the Investigator/Sponsor to immediately notify IRBs should immediate action be required to protect subjects' safety.

The IRB should receive complete, analyzed information with a recommended plan to minimize the risks associated with the event(s) reported and an indication of whether subjects should be provided additional information that may impact their willingness to participate. The timing for receiving these reports (immediate, quarterly, or at the time of continuing review) should be described in the data safety monitoring plan.

In order to review unanticipated or adverse events, the data safety monitoring committee must evaluate the following:

- what was the level of severity?
- was the event unanticipated?
- has this event occurred before, and if so, how often?
- what is the "n" for individuals receiving the intervention?
- was the event related to the protocol procedure(s)?

The IRB should receive only reports of those events that have been determined to have a potential negative impact on subject safety. Therefore, the focus should be on the serious, unanticipated events that are reasonably related to the study procedure.

IRBs have a greater responsibility and ability to evaluate adverse events at the sites over which they have purview. They are in a position to require immediate action to safeguard subjects at their own sites. For the review of internal adverse events for which the local IRB has purview, the Principal Investigator is initially responsible for evaluating the impact of the event, describing any necessary steps to prevent or minimize the occurrence of that event in the future, and reporting his/her findings to the local IRB. If the local researcher does not submit complete information to the IRB, that IRB has the authority to require additional information that will facilitate an assessment of the impact of that event on the safety and welfare of the subjects participating at the local site(s).

In contrast, IRBs have limited knowledge of the Principal Investigator and the local context for external events. In order to assess external adverse events, the IRB needs complete information about the context of the event and an analysis of its relevance and importance to the ongoing study. Rather than receiving numerous free-floating individual external adverse event reports, an IRB should receive an aggregate report with an analysis and conclusion at intervals appropriate to the level of risk.

The role of the IRBs, therefore, should not include the review of individual reports from external sites. The role of IRBs should be limited to fully examining and acting upon local events where the Principal Investigator has done the initial evaluation, proposed procedures to minimize the risk, and has provided complete information for consideration, allowing the IRB to act in an informed manner. As we have previously suggested and reiterate below, review of data from external events should be performed in accordance with an appropriate plan involving one or more persons or a study-specific panel such as a Data and Safety Monitoring Committee, established by the protocol Sponsor/Investigator.

How does that role differ from the current role of IRBs?

This approach differs from the current role IRBs play because the focus of the IRB will switch to ensuring the implementation of an appropriate data safety and monitoring plan at the time of initial review rather than the ongoing review of individual external adverse or unanticipated events. This approach would improve human subjects' protections.

The role of IRB review of external events should be quite different. The IRB should only receive and review aggregate, analyzed reports of external adverse events and be able to review them in the context of implementing changes required to protect human subjects enrolled in that research protocol. This would require central review of all events. Currently, IRBs are receiving information of limited value in determining how best to protect the rights and welfare of subjects. Multiple reports of the same events are often received with little to no reference on the implementation and adjuvant therapies that were associated with the event. Reports are submitted that do not clearly define how the investigational agent was administered, what concomitant therapies were administered, whether the participant was receiving a placebo, whether underlying conditions were present, and a variety of other pieces of information that must be available for an IRB to make an informed analysis.

Should IRB responsibilities for multi-site trials differ from those for single-site trials?

Yes. A summary of the multi-site clinical trials' adverse/unanticipated events should be prepared by a centralized group with the scientific expertise and the charge to evaluate all information regarding reported events. Issues such as stopping a study, changing a procedure, eliminating an agent, or providing additional information to subjects should be the responsibility of this review group in collaboration with the Sponsor/Investigator. The FDA and local IRBs should receive the aggregate report with guidance on how to apply that information to their local populations. The role of IRBs should be to evaluate the impact of aggregate information provided to them, apply that information to the local populations, and take whatever actions are deemed necessary.

Question 2. The types of adverse events about which IRBs should receive information.

What types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs? For example, should IRBs generally receive information only about adverse events that are both serious and unexpected?

The reason IRBs exist is for the protection of research subjects, particularly those at the local research site. Therefore, the IRB should be primarily concerned with, and only receive reports of, individual adverse events that occur at the institution for which the IRB is the IRB of record, and then only when the event meets one or more of the following conditions:

- The event is serious and unanticipated.
- The event indicates an increase in the potential risk to the subjects.
- The event requires revision of the protocol, consent documents, or the investigator's brochure.

The IRB should be provided with external reports such as those produced by a Data and Safety Monitoring Board or from a Sponsor's Medical Monitor. In addition, the IRB should receive only those adverse event reports from non-local sites when the report indicates a revision of the protocol, consent documents, or the investigator's brochure or when the report identifies unanticipated problems that may affect subjects enrolled at the local site.

All reports of adverse events should be accompanied by an analysis that describes the nature of the event and the presumed reason why it occurred, a review of actions taken as a result of the event, and recommendations for actions, if any, that are necessary as a result of the event. In all cases, the IRB should have the authority to require additional information and/or analysis of the event reports.

Are there circumstances under which IRBs should receive information about adverse events that are not both serious and unexpected (e.g., if the information would provide a basis for changing the protocol, informed consent, or investigator's brochure)?

This information should be provided at the time of continuing review for each protocol. It should be provided in aggregate form, with appropriate numerators and denominators so that the IRB can make an informed determination about whether the protocol, consent process, or investigator's brochure should be modified.

> *In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or at another site?*

Yes, the criteria for reporting adverse events to an IRB should differ depending on whether the event occurs at the IRB's site or at an external site. When a study has multiple sites, the processes for reporting and review of adverse events should include central reporting of all adverse events to the Sponsor. The reports should undergo analysis by an appropriately established committee, such as a data monitoring committee (DMC). An aggregated summary report of that analysis should be sent to all reviewing IRBs. Local events that meet the criteria presented above should still be reported to the local IRB so that the IRB may take necessary action at the local level.

Question 3. Approaches to providing adverse events information to IRBs.

> *There seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects. What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects? For example, if prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB's ability to make useful determinations based on the adverse event information it receives? If so, what kinds of information should be included in consolidated reports? And when should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent, or investigator's brochure due to adverse events experience)?*

The current system of submitting all AEs from all sites to all investigators and their respective IRBs is inefficient and inundates investigators and IRBs. These reports currently undergo redundant reviews by many IRBs, often without sufficient data or the expertise of DMCs.

ARENA proposes that all multicenter clinical trials have an appropriate data and safety monitoring plan and that IRBs receive only relevant data that will enhance the protection of research subjects. The ideal plan would establish a committee comprised of experts in the disease or condition under investigation. Such a DMC would be responsible for review of any serious unanticipated problems and any anticipated adverse events that exceed the severity or magnitude expected in the targeted research population.

A DMC's analysis might determine that an AE requires prompt notification to all participating investigators. This might be due to increased risk(s), or new information that may impact subjects' present or future health The DMC would also provide guidance regarding the recommended actions that should be taken by the investigator. These recommendations should include:

- specific language that describes the AE in clear, non-technical terms,
- modification of the protocol treatment or procedures within a designated timeframe,
- guidance for the revision of consent documents for currently enrolled and future study subjects,
- notification of those who have completed the study treatment of the new risks, and,
- notification of the IRB.

We propose that aggregate AE data regarding events that the DMCs determine do not increase the risk to subjects be made available to investigators as part of an annual progress report. This report should comprise a summary of the DMC's general assessment and recommendations relevant to continuing the study.

Finally, we propose that investigators receive only serious, unanticipated and reasonably related AE reports that the DMC concludes are needed to protect clinical trial subjects. Under this system, PIs would have the information needed to take immediate action to protect research subjects. This focused notification of only meaningful AEs would be more efficient and effective than the system currently in place because it would eliminate redundant review of AEs by multiple IRBs, and would better protect research subjects in clinical trials.

Who should provide such reports?

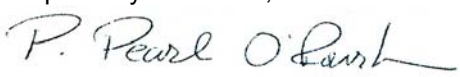
The DMC should provide the adverse event reports to the PI, and the PI should provide them to the IRB.

Q. Should the approach to providing IRBs adverse event reports be the same for drugs and devices?

Yes, the approach to adverse event reports for drugs and devices should be identical.

Thank you again for the opportunity to share these comments. ARENA will also submit written comments by the April 21, 2005 deadline.

Respectfully submitted,



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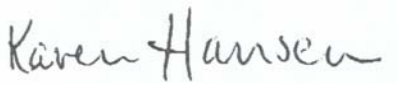

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